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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,272	11/22/2004	Domenico Maglione	10500-008	4002

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/507,272	MAGLIONE ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 07.27.06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received July 27, 2006. Claims 1-15 are canceled. Claims 16-35 are pending and currently under examination.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

The rejection of claims 16-22 under 35 U.S.C. 103(a) as being unpatentable over Ziche et al. (1997 Laboratory Investigation 76(4): 517-531) in view of Failla et al. (2000 J. Invest. Dermatology 115(3): 388-395) was previously withdrawn in the March 27, 2006 Office action. However, upon reconsideration of Applicants' amendments and remarks, the rejection of the claims under 35 U.S.C. 103(a) is believed to be appropriate.

Priority: The priority date is March 5, 2002.

Objections and Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-22, 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims read on a method of treatment of a state comprising preparing an angiogenesis promoting medicament comprising type I Placental Growth Factor (PLGF-1) and administering said medicament to treat the state, the state selected from the group stated in the claim. Thus, the claims read on any subject and/or mammal which is undergoing the recited state, i.e. diseases and pathological alterations involving the cutaneous or subcutaneous connective tissue, scleroderma, and early skin aging to due exposure to atmospheric aggressive agents or to protracted solar irradiation. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to a method of treatment of any subject undergoing alterations involving the cutaneous or subcutaneous connective tissue because different subjects and different types of subjects require different therapeutic amounts even if undergoing the same disease and/or disorder.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of

experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case the quantity of experimentation would be large since there are myriad mammalian subjects and effective amounts of PLGF-1 to choose from. The amount of guidance in the specification is minimal with regard to which subjects will undergo the recited states and which dosages are the most effective in treating alterations involving the cutaneous or subcutaneous tissue. The working examples provided in the specification involve the treatment of hairless mice, scleroderma in mice, and exposure of skin to aggressive agents in adult humans. No working examples are present of administering an effective amount of PLGF-1 to other mammalian subjects that may undergo or suffer from alterations involving the cutaneous tissue. The nature of the invention is such that many other types of mammals may suffer from alterations involving the cutaneous tissue and the administration of PLGF-1 may or may not help in the treating the state, depending on the effective amount. The state of the prior art is that an effective amount of PLGF-1 that is administered to treat hairless mice may or may not be effective to treat hair loss in a human. The relative level of skill in this art is high. The predictability as to the effect of PLGF-1 when administered to other types of mammalian

subjects that undergo alterations involving the cutaneous or subcutaneous connective tissue is uncertain.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 19 has been amended to recite a particular state. The introduction of a particular state is not supported in the instant and/or original specification and therefore constitutes as new matter added to the claim.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-35 are rejected again under 35 U.S.C. 102(b) as being anticipated by Ziche et al. (1997 Lab. Invest. 76(4): 517-531). Ziche et al. teach PIGF-1 protein was purified mostly as homodimeric glycosylated protein and was approximately 0.17 mg/l of conditioned medium (p. 528; claims 30-35). Densitometric scanning of the stained gels revealed that 0.4%, 86.3%, and

13.2% of the total protein corresponded with monomeric, dimeric, and trimeric forms of PIGF-1, respectively (p. 518; claims 30-35). On page 528, col. 2, Ziche et al. teach affinity-purified PLGF-1 antibodies were obtained from the immune rabbit serum as described by Maglione et al. (1991 PNAS 88: 9267-9271). As described in the Maglione et al. reference, two rabbits were immunized with a total of 300 ug antigen, therefore meeting the dosage requirements of claims 30-31 (p. 9268 Maglione et al.).

In their remarks received July 27, 2006, Applicants assert that as amended, claims 30-35 are not anticipated by Ziche et al., which is silent as to topical compositions as are now claimed. Applicants note that the topical nature of the composition, first stated in the preamble, is a limitation of these claims. While Ziche et al. pertains to angiogenesis in rabbit cornea and chorioallantoic membrane, it does not teach, nor suggest, a topical composition. Applicant's arguments have been fully considered but they are not persuasive. Statements of intended use or purpose are not limiting to the interpretation; therefore, regardless of claims 30-31 recitation of a pharmaceutical composition comprising PLGF-1 for topical use, the instant claims are still anticipated by Ziche et al. because Ziche et al. teach a solution comprising PLGF-1 in active dimeric and multimeric form and said solution is inherently a topical composition.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-22, 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ziche et al. (1997 Laboratory Investigation 76(4): 517-531; previously cited) in view of Failla et al. (2000 J. Invest. Dermatology 115(3): 388-395; previously cited). The teachings of Ziche et al. are outlined above. While Ziche et al. teach promotion of angiogenesis with PLGF-1, Ziche et al. do not teach the application of PLGF-1 in the treatment of a state selected from the group consisting of diseases involving cutaneous or subcutaneous connective tissue, scleroderma, and early skin aging due to exposure to atmospheric aggressive agents.

Failla et al. (2000 J. Invest. Derm. 115(3): 388-395) teach PLGF-1 is induced in human keratinocytes during wound healing. Fallia et al. teach PLGF-1 is expressed *in vivo* by migrating keratinocytes at the wound site (p. 391). The involvement of PLGF in wound healing was tested by analyzing its expression in human full-thickness wounds *in vivo* (p. 391). Failla et al. teach their data demonstrate that keratinocytes are a source of PLGF during wound healing *in vivo* and indicate a role for PLGF-1 in the neoangiogenesis process associated with cutaneous wound repair (p. 388, abstract).

It would have been obvious to a person having ordinary skill in the art to formulate the PLGF-1 composition of Ziche et al. and use it in promoting angiogenesis in the treatment of an alteration involving skin tissue (claims 16-22) in view of Failla et al. because Failla et al. teach and suggest a role for PLGF-1 in the neoangiogenesis process associated with cutaneous wound repair. One of ordinary skill in the art would be motivated to apply the PLGF-1 composition of Ziche et al. in view of Failla et al. to a skin alteration and expect it to have a reasonable level of success because Failla et al. disclose PLGF-1 has a role in cutaneous wound repair and its addition to a skin alteration would help to expedite the healing process.

It would also have been obvious to a person having ordinary skill in the art to apply the PLGF-1 composition of Ziche et al. and use it for the cosmetic treatment of an adult (claims 23-26) in view of Failla et al. because Failla et al. teach and suggest a role for PLGF-1 in the neoangiogenesis process associated with cutaneous wound repair. One of ordinary skill in the art would be motivated to apply the PLGF-1 composition of Ziche et al. in view of Failla et al. for the treatment of natural skin again and hair loss in an adult and expect it to have a reasonable level of success because these conditions are known in the art to be skin diseases and/or disorders and Failla et al. disclose PLGF-1 has a role in cutaneous wound repair and its addition to a skin alteration would help to expedite the healing process

In their arguments received January 19, 2006, regarding the rejection of claims 16-22 under 35 U.S.C. 103(a) as being unpatentable over Ziche et al. (1997 Laboratory Investigation 76(4): 517-531) in view of Failla et al. (2000 J. Invest. Dermatology 115(3): 388-395), Applicants first note that the target diseases of the instant invention are related to alterations of the connective tissues and are characterized by fibroblast activation and excessive production and deposit of sclerosed collagen with formation of fibrosis and calcification zones. Applicants assert Ziche discloses the ability of PLGF-1 to elicit angiogenesis in the chicken cornea and in the chicken chorioallantoic membrane, which is a simple biological activity of PLGF-1. Regarding the Failla et al. reference, Applicants assert Failla et al. teaches that native PLGF is induced in human keratinocytes during wound healing and demonstrates that PLGF plays a role in the neoangiogenesis process associated with wound repair. Applicants further assert that the definition of a "wound" is different from the pathological states of scleroderma and the other

connective tissue diseases according to the invention. Wounds are normally due to external agents, which are not comparable to the impaired metabolism resulting in the production and deposit of sclerosed collagen in the connective tissues. Applicant's arguments have been fully considered but they are not persuasive.

As amended, instant claim 16 is drawn to a method of treatment of a state comprising administering PLGF-1 to treat a state selected from diseases and pathological alterations involving the cutaneous or subcutaneous connective tissue, scleroderma, and early skin aging due to exposure to atmospheric agents or to protracted solar irradiation. It is known in the art that a wound is a disruption in the continuity of cells. As noted above, Applicants assert wounds are normally due to external agents. Claim 16 recites a state wherein skin is exposed to atmospheric aggressive agents, i.e. acidic rain, hail, or to protracted solar irradiation, which may result in a skin wound or skin burn, respectively. Therefore, the states as recited in instant claim 16 can be considered to be a wound to the skin and/or alteration to the cutaneous tissue. Therefore, one of ordinary skill in the art would be motivated to use the composition of PLGF-1 of Ziche et al. to treat a skin alteration because Failla et al. disclose a role for PLGF-1 in the neoangiogenesis process associated with a skin alteration, i.e. a cutaneous wound repair.

In their remarks received July 27, 2006, Applicants also assert the biological property of PLGF-1, i.e. the ability of PLGF-1 to elicit angiogenesis as disclosed by Ziche et al., cannot be confused with a pharmacological, therapeutic effect that necessarily implies the capability of correcting and recovering an abnormal situation (in particular, one involving connective tissue alterations as in the instant invention). However, as explained in the remarks above, the Failla et

al. reference supplements the Ziche et al. reference and indicates that PLGF-1 does have a pharmacological and therapeutic effect in wound healing.

Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carmeliet et al. (WO 0156593). Carmeliet et al. teach enhanced revascularization of acute myocardial infarcts by administration of PLGF-1 (p. 17). In working example 3, Carmeliet et al. show the treatment of infarcted mice with PLGF dimer with different dosage units of 715 ng/day and 3.5 ug/day, respectively (p. 18, line 10). Carmeliet et al. also disclose dosages of PLGF composition that can be administered. For example, examples of therapeutically effective amounts of PLGF composition are preferably an amount of about 2 to 2,000 ug per kg of body weight of mammal to be treated. Therefore, depending on the body weight of the subject to be treated, the amount of PLGF-1 administered can vary. On pages 10-13, Carmeliet et al. also disclose various suitable pharmaceutical carriers, surfactants, and agents that can be used to formulate various forms of PLGF-1 compositions, such as solutions, emulsions, pellets, and powders. Furthermore, the PLGF-1 compositions can be administered by various means including oral, intranasal, or parenteral administration (p. 9 line 25). Carmeliet et al. do not teach PLGF-1 to be in a composition in an amount from 50 ug to 30 mg per unitary dose and/or in an amount from 0.1 mg to 10 mg per gram for topical use.

It would have been obvious to a person having ordinary skill in the art to formulate a composition comprising PLGF-1 as an active principle in dimeric form, and in an amount of about 2 to 2,000 ug per kg of body weight of subject (claims 30-35) with a suitable pharmaceutical carrier and/or agent for topical use or any other suitable mode of administration

in view of modern pharmaceutical practice because Carmeliet et al. teach and suggest the use of compositions comprising PLGF-1 dimer as active principle for improving infarct angiogenesis and arteriogenesis, wherein the PLGF-1 compositions can be formulated into various forms such as solutions.

In their remarks received July 27, 2006, Applicants assert that claims 30-35 as amended are not suggested by Carmeliet et al., which is silent as to topical compositions as are now claimed in instant claims 30-35. Applicants further assert that the topical nature of the composition, first stated in the preamble, is a limitation of these claims. Further, the fact that Carmeliet et al. specify numerous routes of administration (p. 9, lines 22-25) and that these specified routes do not include topical use indicates that a topical composition was not conceived by, and was not suggested by Carmeliet et al. Applicant's arguments have been fully considered but they are not persuasive.

While Applicants have currently amended instant claims 30-35 to recite the limitation of a topical composition, the instant claims are still unpatentable over Carmeliet et al. because one of ordinary skill in the art would recognize that the PLGF-1 compositions of Carmeliet et al. can be formulated into a solution for topical use. This is also exemplified in instant claims 32-33, which indicates that a solution is an acceptable form for a topical composition.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

October 13, 2006

MARYAM MONSHIPOURI, PH.D.
PRIMARY EXAMINER